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SYNTHESIS OF (±)-NORAMBREINOLIDE BY CYCLIZATION OF TRANS-β-MONOCYCLOHOMOFARNESIC ACID

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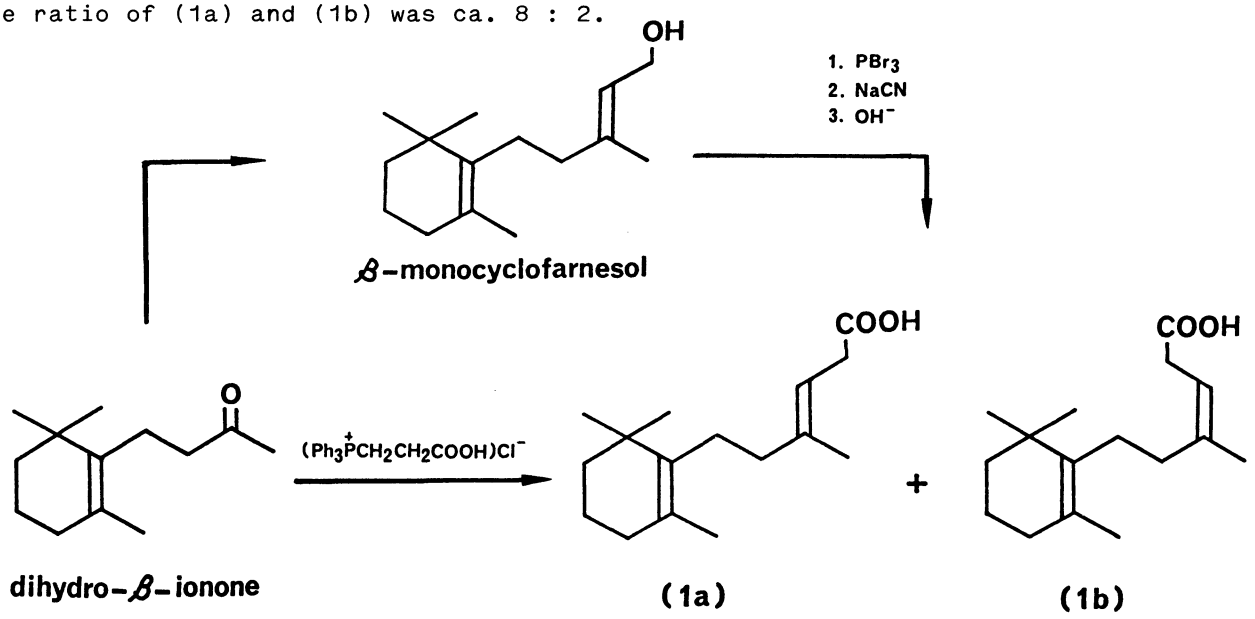
Synthesis of norambreinolide by acid-catalized cyclization of trans-β-monocyclohomofarnesic acid was studied. From the acid norambreinolide was obtained in 57 per cent yield by catalysis of stannic chloride in dichloromethane at -78°C. Isomerization of norambreinolide to norisoambreinolide was observed with a rise of reaction temperature in the presence of stannic chloride.

Norambreinolide (decahydro-3a,6,6,9a-tetramethyl-(3aα,5aβ,9aα,9bβ)-naphtho (2,1-b)furan-2(1H)-one) (2)[1], amber-like odorous compound, has been the object of numerous synthetic studies[2)-5)]. Several methods has been employed to synthesize (2) by the oxidative degradation of naturally occurring labdane-type diterpenes, but little attention has been given to the biomimetic cyclization of polyolefinic carboxylic acid to obtain (2). Only Lucius investigated the acid-catalized cyclization of trans-α&β-monocyclohomofarnesic acid ethyl ester and trans-homofarnesic acid[6)]. Although (2) was not found in the reaction mixture, he suggested the possibility of the initial formation of (2) followed by isomerization to norisoambreinolide (3).

On the other hand, it has been already reported that the cyclization of homogeranic acid gives (±)-trans-tetrahydroactinidiolide stereoselectively in good yield[7)]. Taking these results into consideration, some possibility of synthesis of (2) by cyclization of trans-β-monocyclohomofarnesic acid (4-methyl-6-(2,2,6-trimethyl cyclohexenyl)-3-hexenoic acid) (1a) seemed to remain.

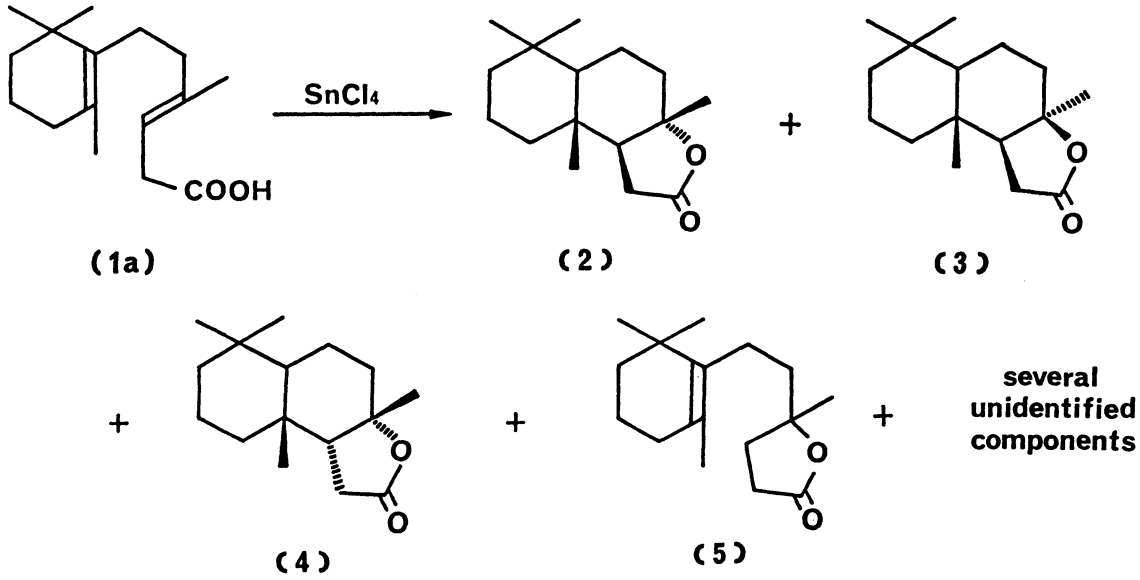
Bromination of trans-β-monocyclofarnesol[8] followed by nitrilation and hydrolysis afforded a mixture of (1a) and its cis isomer (1b) in 56% overall yield. It was also obtained by the Wittig reaction of dihydro-β-ionone and β-carboxyethyltriphenylphosphonium chloride in 71% yield[9]. In both procedures the ratio of (1a) and (1b) was ca. 8 : 2.



Acid, (1a), was purified more than 98% purity as follows. The mixture of (1a) and (1b) was esterified by $TiCl_4$-EtOH, separated by silica gel chromatography (Hexane:AcOEt=99:1)[10], and hydrolized by 10% KOH-MeOH.

Typically the cyclization was carried out by dropwise addition of stannic chloride (2ml) to a stirred dichloromethane solution (3ml) of (1a) (30mg) at -78°C. After the addition, the reaction mixture was stirred at -78°C for an hour and then poured on ice. The product extracted with ether consisted of 76%(2), 2%(3), 10%(4), 1%(5) and 11% several unidentified components. Identification of these compounds was made by the spectral data (^{1}H-NMR, ^{13}C-NMR, MS, IR)[11]. The ratio of these compounds was estimated by peak area measurement of the G.L.C. (OV-101 glass capirally column, φ 0.25mm×50m). The yield of (2) by G.L.C. analysis was 69% and the isolated yield of (2) by crystalization after silica gel chromatography was 57%.

A rise in reaction temperature increased the proportion of (3) in the cyclization product. In the cyclization of (1a) (30mg) in dichloromethane solution (3ml) with stannic chloride (0.1ml) at 20°C for 20min, the product involved 40%(2), 28%(3), 9%(4), 10%(5) and 13% several unidentified components.



Isomerization of (2) by stannic chloride was independently observed to give a mixture of (2) and (3) in ratio of 3:2 under the same condition. Therefore in this type of cyclization, (3) was concluded to be obtained by the isomerization of (2) which was the initial cyclization product.

In this work it was revealed that (2), less stable than (3), can be effectively obtained from trans-β-monocyclohomofarnesic acid under the selected condition. Although the detection of (4), (5), and several unidentified components indicates the possibility of some complicated cyclization routes, the route to give (2) is apparently dominant.

Further details of the cyclization mechanism will be reported together with results of cyclization of isomers and derivatives of (1a).

Reference and Notes

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10) Analytical data of these isomers are as follows;

a) ethyl ester of (1a) : IR(neat) ν =1740cm^{-1}; MS m/e 278 (M^+); ^{1}H-NMR($CDCl_3$) δ=0.99(6H,s), 1.23(3H,t,J=7Hz), 1.61(3H,s), 1.67(3H,s), 2.08(4H,s), 3.03(2H,d, J=6Hz), 4.13(2H,q,J=7Hz), 5.38(1H,t,J=7Hz); ^{13}C-NMR($CDCl_3$) δ =12.3, 16.4, 19.7, 19.8, 27.7, 28.7(two carbons), 32.9, 33.8, 35.0, 40.0, 40.2, 60.3, 115.5, 127.1, 137.0, 139.9, 172.2;

b) ethyl ester of (1b) : IR(neat) ν =1740cm^{-1}; MS m/e 278 (M^+); ^{1}H-NMR($CDCl_3$) δ =1.01(6H,s), 1.25(3H,t,J=7Hz), 1.62(3H,s), 1.79(3H,s), 2.04(4H,s), 3.06(2H,d, J=7Hz), 4.16(2H,q,J=7Hz), 5.32(1H,t,J=6Hz); ^{13}C-NMR($CDCl_3$) δ =12.3, 19.6, 19.9, 23.3, 27.0, 28.7(two carbons), 32.8(two carbons), 33.8, 35.0, 39.9, 60.5, 116.0, 127.4, 137.0, 139.9, 172.5;

11) Analytical data of these compounds are as follows;

a) All the spectra of (2) and (3) were identical with norambreinolide and norisoambreinolide derived from natural source. (2): m.p. 123-125°C

b) (4): IR($CHCl_3$) ν =1760cm^{-1}; MS m/e 250 (M^+); ^{1}H-NMR($CDCl_3$) δ =0.83(3H,s), 0.92(3H,s), 1.11(3H,s), 1.57(3H,s); ^{13}C-NMR($CDCl_3$) δ =18.1, 19.2, 21.8, 22.7, 27.3, 32.5, 32.7, 33.3, 35.9, 37.0, 38.1, 41.9, 46.3, 56.7, 85.5, 175.0;

c) (5): IR(neat) ν =1760cm^{-1}; MS m/e 250 (M^+); ^{1}H-NMR($CDCl_3$) δ =0.99(6H,s), 1.42(3H,s), 1.59(3H,s); ^{13}C-NMR($CDCl_3$) δ =19.5, 19.8, 22.6, 25.3, 28.6(two carbons), 29.2, 32.8, 32.9, 35.1, 39.8, 41.0, 86.9, 127.7, 135.8, 176.9;

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